# $Ca^{2+}$-induced Calcium-Release in a Rat Ventricular Cell ---- A Model Study

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*Abstract*-**A computer model is developed for the characterization of $Ca^{2+}$-induced calcium release (CICR) from the sarcoplasmic reticulum (SR) in the rat ventricular cell. The fluid compartment model is configured to describe the trigger $Ca^{2+}$ influx ($I_{Ca,L}$) through the membrane of the sarcolemma (SL); the diffusion of $Ca^{2+}$ throughout a small cleft space, which is located between the SL and the junctional sarcoplasmic reticulum (jSR); and a distribution of five ryanodine (Ry)-sensitive $Ca^{2+}$ release channels called the "$Ca^{2+}$-release complex". Each Ry-receptor controlled channel (or RyR channel) is characterized by a 4-state Markovian kinetic scheme. Two $Ca^{2+}$ ions are required to bind to RyR for channel activation, and one $Ca^{2+}$ ion is required for channel inactivation. The model provides both sufficient $Ca^{2+}$-release gain and graded release behavior. The complete model is used to simulate the whole-cell $Ca^{2+}$ transient data, evoked in voltage clamp test. We also studied the linear relationship between the rising rate of the $Ca^{2+}$ transients and the peak trigger $I_{Ca,L}$. The model results suggest that this relationship is the indirect result of 2nd-order RyR activation dynamics, filtered by fluorescent indicator dye.**

Keywords – ***CICR, $Ca^{2+}$ graded release, Computer model.***

## I. Introduction

A transient rise in intracellular $Ca^{2+}$ concentration results in contraction of cardiac muscle. An important characteristic of $Ca^{2+}$ release in cardiac muscle is that it is not directly dependent upon voltage depolarization. Rather, it is the local $Ca^{2+}$ concentration around the RyR channels of the jSR membrane that causes the opening of the RyR channel and subsequent $Ca^{2+}$ release [1]. The jSR stores large amounts of $Ca^{2+}$ in the resting state. This phenomenon is commonly called "calcium-induced calcium release" or CICR [2]. Two fundamental properties are related to CICR, namely graded behavior and high gain [1]. Graded behavior refers to the experimental fact that SR $Ca^{2+}$ release is proportional to the amplitude of trigger $I_{Ca,L}$ influx, and high gain relates to the fact that cytosolic $Ca^{2+}$ concentration is much larger when $Ca^{2+}$ release from the jSR occurs, compared to the case that $Ca^{2+}$ release from the jSR is inhibited.

## II. Model development

Figure 1 shows the structure of the fluid compartment model. We model the diffusion of $Ca^{2+}$ throughout a cylindrical cleft space using partial differential equations (PDEs). $Ca^{2+}$ enters the cell and diffuses within the cleft space and reaches the receptors on the other side of the cleft, the cluster of RyR channels distributed on the jSR. $Ca^{2+}$ then accumulates at the "mouths" of the RyRs and activates the jSR release channels. $Ca^{2+}$ diffuses from the cleft space into the bulk myoplasm. All major $Ca^{2+}$ buffers are considered in the fluid compartment model (not shown in the figure), including fluorescent dye and calmodulin distributed both in the myoplasm and in the cleft space, troponin in the bulk myoplasm, and calsequestrin in the jSR. Active and passive $Ca^{2+}$ pumps and exchangers, which are embedded either in the SL membrane or in the SR, are also considered in the model.

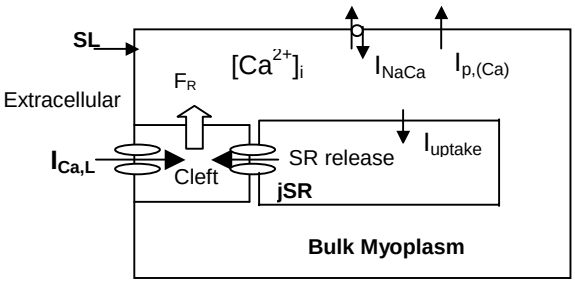


Fig 1. Illustration of the $Ca^{2+}$ release model

Morphological studies indicate that a single DHP-sensitive $I_{Ca,L}$ channel is coupled with multiple RyRs [3]. We therefore configure one $I_{Ca,L}$ channel facing a distribution of RyRs on the jSR surface membrane. Specifically, the central RyR sensing site is surrounded by other 4 identical RyRs in a circular pattern (i.e., 5:1 RyR/DHPR stoichiometry). The 4-state gating scheme for each RyR channel is illustrated in Fig 2. The activation gate ($P_O$) is opened by the binding of two $Ca^{2+}$ ions, and the inactivation gate ($P_I$) is controlled by the binding of a single $Ca^{2+}$ ion.

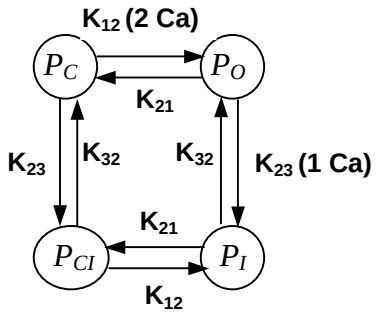


Fig 2. Schematic diagram for the 4-state Ry-sensitive $Ca^{2+}$ release channel. $K_{12}$: RyR Ca-dependent activation rate, $K_{21}$: RyR deactivation rate, $K_{23}$: RyR Ca-dependent inactivation rate, $K_{32}$: RyR repriming rate.

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**Abstract**

**Subject Terms**

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2

## III. RESULTS

We have previously modeled the L-type $Ca^{2+}$ current channel [4]. Our current study is focused on the response of the RyR channel model to measured $I_{Ca,L}$ data.

### A. *Graded $Ca^{2+}$ Release*

A simulation of cytosolic $Ca^{2+}$ transient at the 10 mV depolarization level is shown in Fig 3A. The model provides excellent fit to measured calcium transient data at this voltage level. Quantitatively, graded $Ca^{2+}$ release is illustrated in Fig 3B. From the I-V relationship between peak amplitude of $I_{Ca,L}$ and depolarization voltage, it is clear that peak $I_{Ca,L}$ current is largest near 10 mV and decreases with more positive depolarizations. Correspondingly, peak amplitudes of model-generated $[Ca^{2+}]_i$ over a wide range of depolarizations ($10 \le V \le 60$ mV ) show a similar behavior, i.e., maximum values of $[Ca^{2+}]_i$ decrease from 1.0 $\mu M$ to 0.25 $\mu M$ , as potential is made more positive. The "mirror-image" behavior of $[Ca^{2+}]_i$ to the trigger $I_{Ca,L}$ in the I-V plots confirms the graded $Ca^{2+}$ release characterized by the computer model.

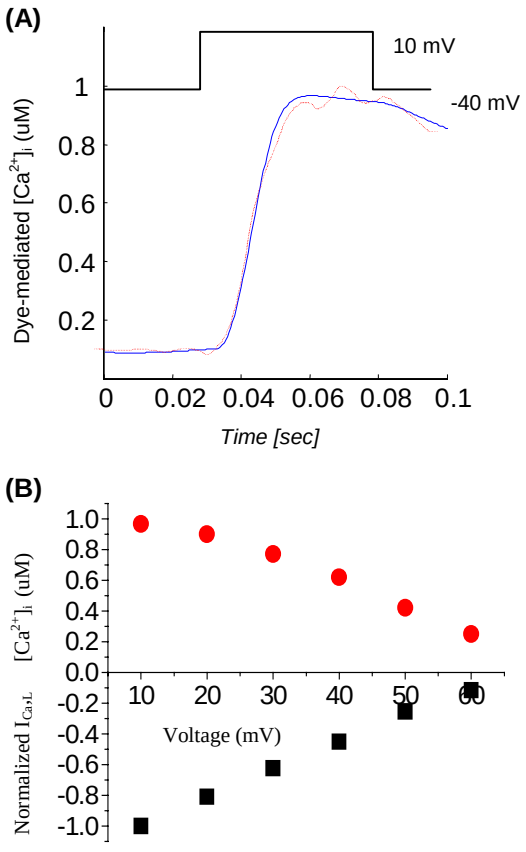


Fig 3. (A). Model simulation (solid) and data (dotted) of cytosolic $Ca^{2+}$ transients at simple depolarization protocol of 10 mV; (B). $I_{Ca,L}$-V and $[Ca^{2+}]_i$-V mirrored curves representing graded $Ca^{2+}$ release.

### B. *High Gain of $Ca^{2+}$ Release*

The gain or amplification factor due to CICR can be obtained by calculating the ratio of the average integrated RyR flux to the average integrated DHPR flux. Alternatively, the gain of $Ca^{2+}$ release by opening of RyRs can be computed as the ratio of the peak $[Ca^{2+}]_i$ in the presence of CICR to the peak $[Ca^{2+}]_i$ which resulted from the trigger $I_{Ca,L}$ alone.

We used both definitions to examine CICR resulting from the opening of RyRs and $Ca^{2+}$ release from the jSR. The first method yields a RyR/DHPR flux ratio of 7.98, whereas the second method provides a gain factor of 8.04. By either method, the calculated CICR amplitude of approximately 8 is sufficient and is similar to that reported by Stern [1].

### C. *Systematic Study of $Ca^{2+}$ Release*

We have also studied the input-output relationship of the $Ca^{2+}$ release system. The maximum rate of rise of the cytosolic $Ca^{2+}$ transient and the peak amplitude of $I_{Ca,L}$ input current are used as global measure of the output and input variables of the SR $Ca^{2+}$ release system respectively [5]. Our model predicts a linear relationship as well, but only when $Ca^{2+}$ indicator dyes are present. However, it is not safe to conclude that a single $Ca^{2+}$ ion is enough to activate RyR in terms of such relationship. In fact, our input-output linear relationship was achieved by the RyR model of 2nd order $Ca^{2+}$-binding activation (Fig 2). Further model studies indicate that $Ca^{2+}$-buffering by the fluorescent indicator dye has a very important effect, namely, it distorts the quadratic relationship from the RyR model and makes the overall dye-mediated $Ca^{2+}$ transient appear linearly related to the input $I_{Ca,L}$.

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